# Immune Response Modifiers Pathway Example

Sunday, November 9, 2008

# Immune Response Modifier Pathway

# WT-1 vaccine for minimal residual disease in WT-1+ Acute Myeloid Leukemia & Ovarian Cancer

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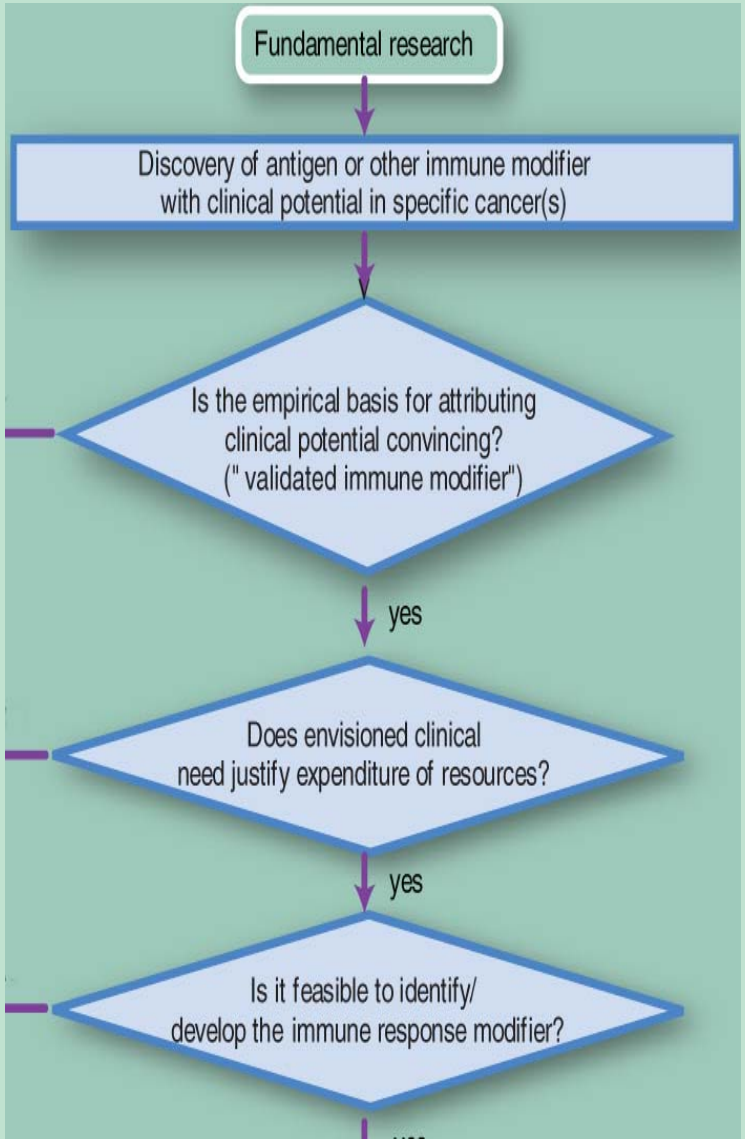
# Immune Response Modifier Pathway: Challenges for Vaccine Development

- Biology
  - Immune tolerance
  - Immune incompetence
    - Age
    - Lympholytic chemotherapy
  - Intrinsic mechanisms actively limiting T cell expansion
    - Checkpoint blockade
    - Regulatory T cells
    - Inhibitory cytokines
    - Limiting T cell growth factor concentrations
  - Cancer cell immune suppression
- Formulation
  - Preference for T cell responses
  - Preference for continued vaccinations
- Regimen
  - Multiple components to circumvent above biological limitations
    - (Adjuvants & Immune Response Modifiers)
      - Sparse availability of component agents
      - Concurrent development of several unapproved agents

# Immune Response Modifier Pathway: Credentialing: Scientific validation




- 27 ABSTRACTS IN VACCINE SESSION
- 12 SHARED ANTIGENS
- **All with Scientific Validation**
  - AFP (alpha fetoprotein)
  - CAIX (Carbonic anhydrase-9)
  - EGFRvIII
  - HER2
  - HPV
  - FAK (focal adhesion kinase)
  - Melanoma — various
  - MUC1
  - p53 — non-mutant
  - PSMA (prostate specific membrane antigen)
  - TMPRSS2 ERG fusion protein
  - TYRP2 (tyrosine related protein 2)

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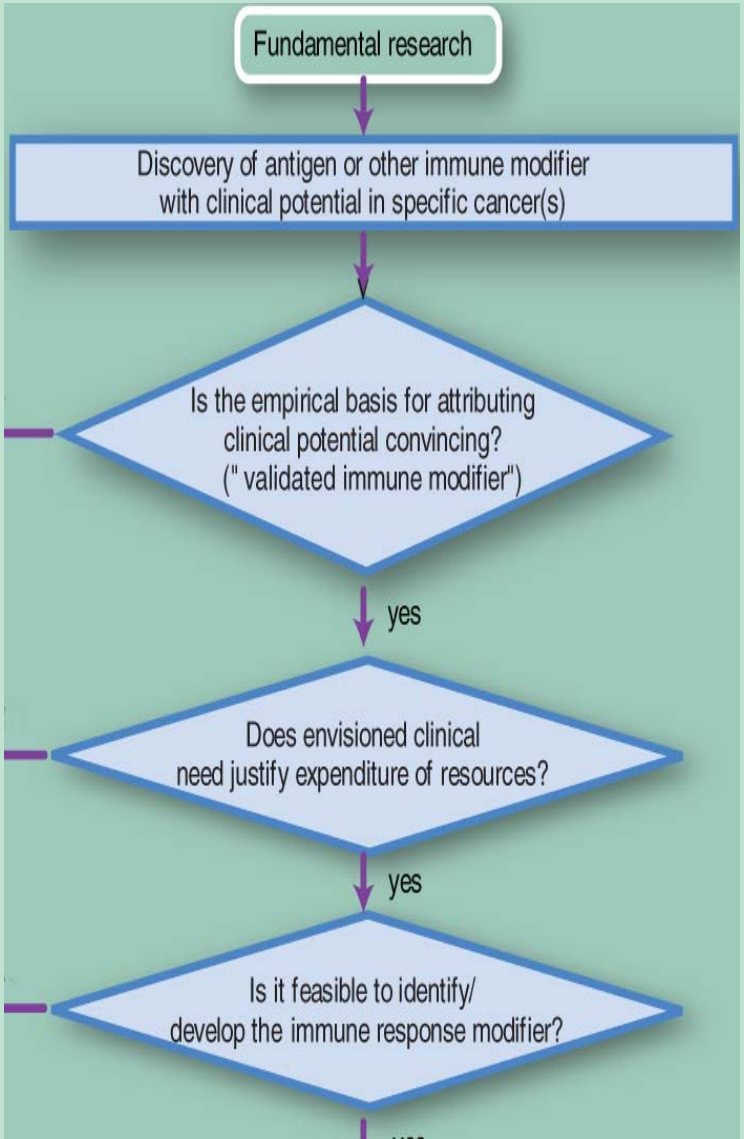


- 5 ADJUVANTS FOR SHARED ANTIGENS
- **All with Scientific Validation**
- Dendritic cells (DC) x 6
- GM-CSF x 4
- HSP x 3
- KLH x 1
- CpG x 1

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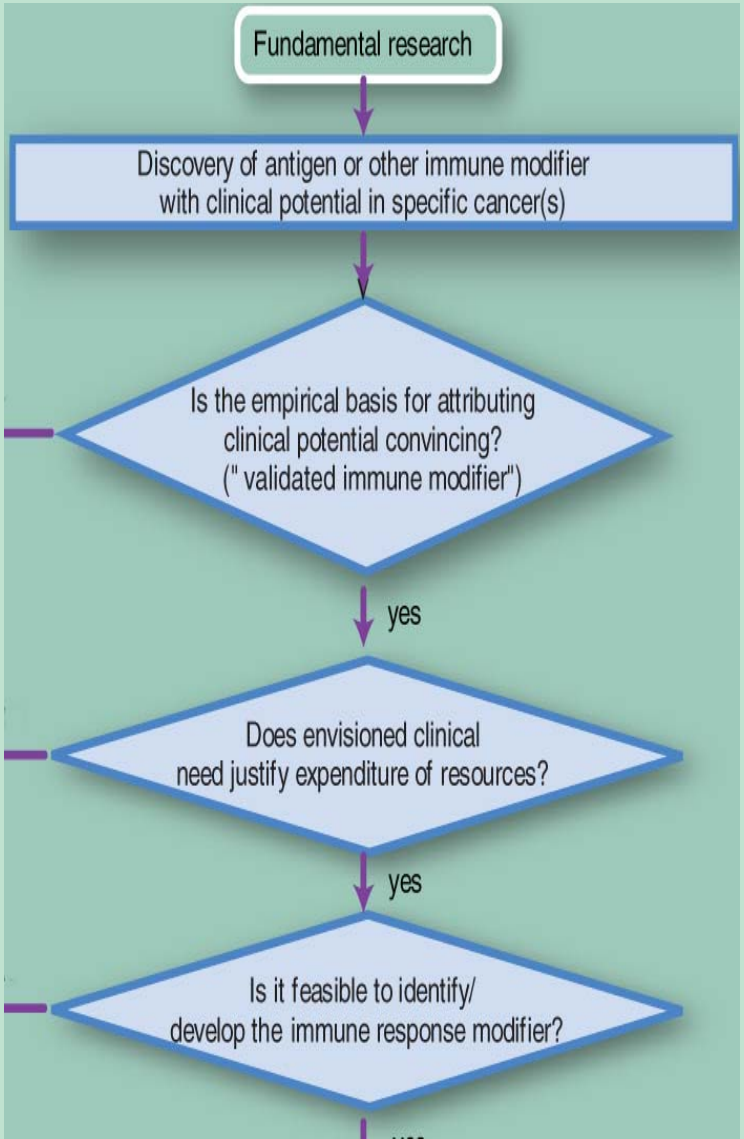


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- **All with Scientific Validation**
- Dendritic cells (DC) x 6
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- Availability of only a limited number of adjuvants is a MAJOR problem!

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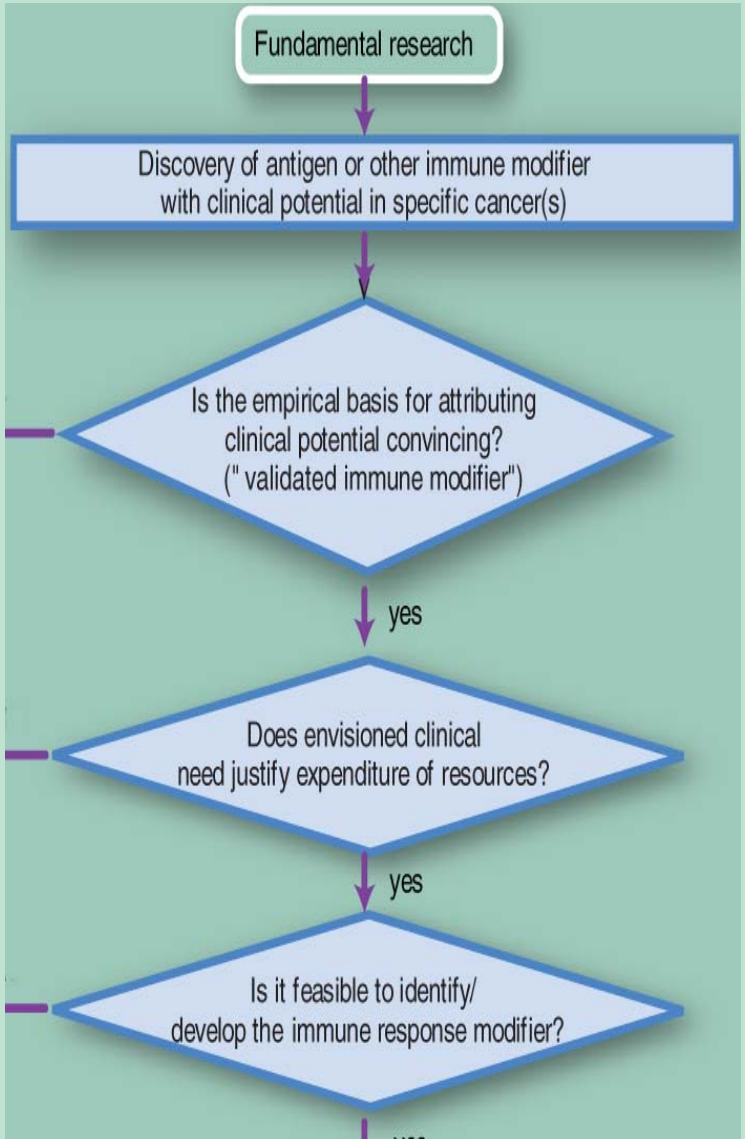



- 9 ADDITIONAL APPROACHES
- **All with Scientific Validation**

- 2 Allogeneic Tumor Approaches
- (Multiple Shared Antigens)
  - Allogeneic cancer cells with anti-TGF-b2
  - Allogeneic or autologous tumor immune check point inhibitors

- 5 Autologous Tumor Approaches
- (Multiple Unique Antigens)
  - Autologous cancer cells with DC fusion
  - Autologous cancer with PDT (photodynamic therapy)
  - Autologous HSP 96
  - Autologous tumor expressing gp-96-Ig to mediate cross-priming
  - Systemic IL2 + IL12

- 2 Infectious Disease Vaccine Approaches
  - Hematopoietic cell transplant with donor immunization (CMV)
  - Replicating Adenovirus (HIV)

# Immune Response Modifier Pathway:
## Credentialing: Scientific validation

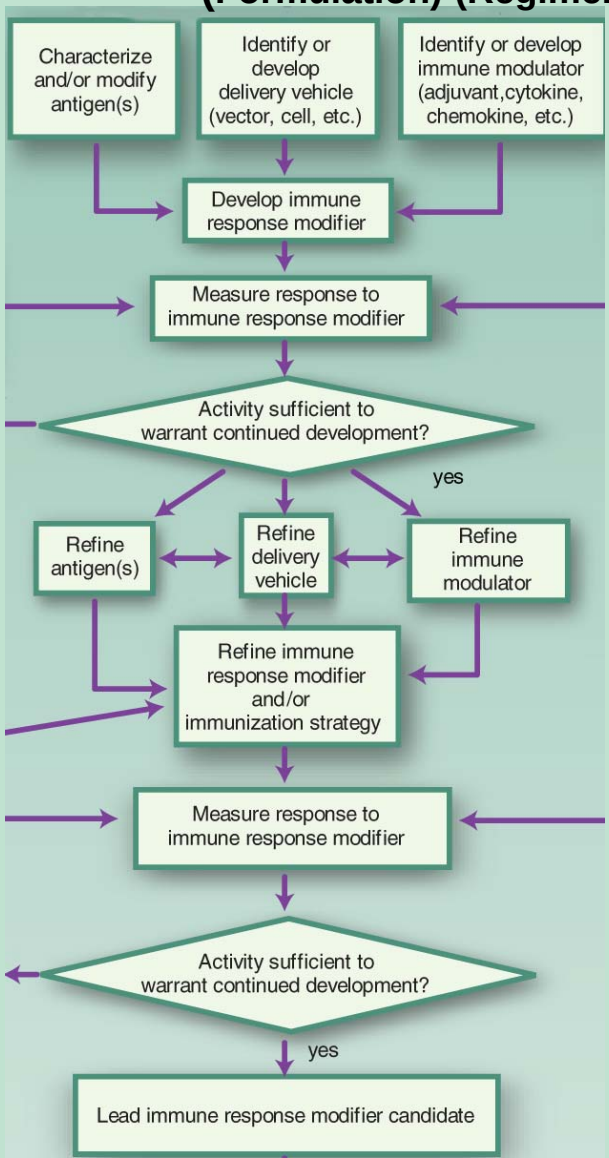
## 27 ABSTRACTS
## 22 APPROACHES TO AUGMENT IMMUNITY

- Anti-TFG-b2
- Alpha virus
- Calreticulin plasmid co-expression
- DC activators
- DC targeting Ab
- DC tumor fusions
- Gleevec + PDT
- Glycosylated & anchored modified peptides
- GM-CSF fusion protein
- GP96-Ig to mediate cross priming
- Heterologous protein prime/boost
- HSP 70
- HSP 96
- IL2 + IL12
- Immune check point inhibitors
- KLH + protein
- Plasmid/Adv prime/boost
- SCT donor immunization
- Tim-1 Ab
- TRAIL + Chemotx
- Replicating Adenovirus
- Vectors containing TLR & CD40 signaling

# Immune Response Modifier Pathway:
## Creation of Modality

**Antigen – Delivery – IRM**

**(Formulation)-(Regimen)**

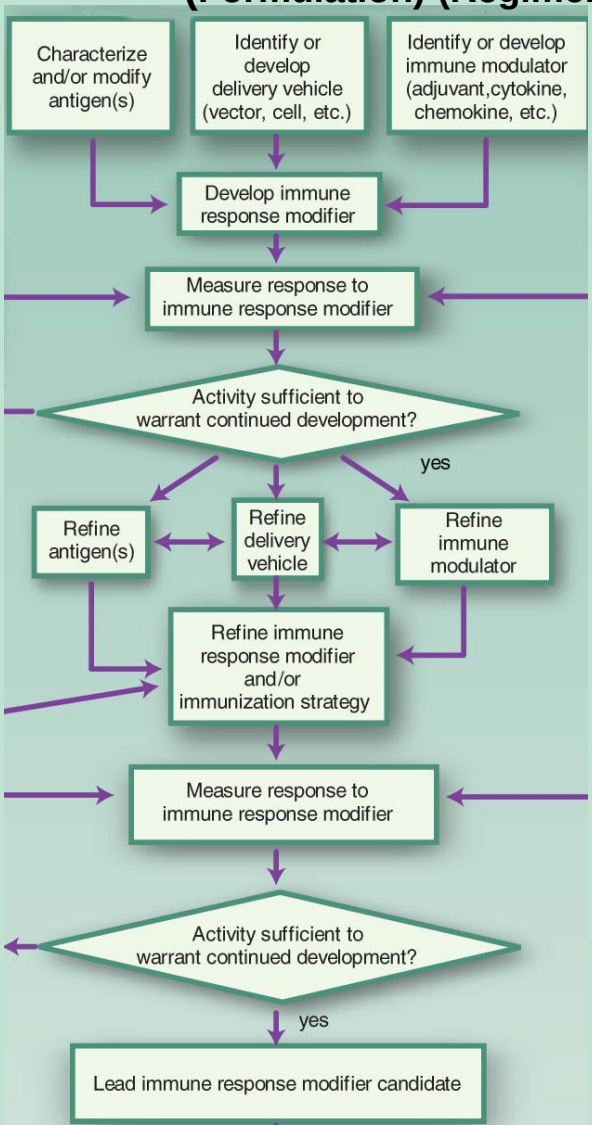



- Example of “Creation of Modality”
- 27 Vaccine Abstracts
  - 12 shared antigens + 7 whole tumor
  - 5 adjuvants
  - 22 approaches to augment immunity
  - >2,000 combinations

# Immune Response Modifier Pathway:
## Creation of Modality

**Antigen – Delivery – IRM**

**(Formulation)-(Regimen)**




- Example of "Creation of Modality" "Vaccine using a shared antigen"
- **What vaccine has the highest potential for success?**
  - **Antigen?**
  - Formulation?
    - Delivery vehicle
    - Vector/cell/etc
    - Adjuvant
  - Regimen?
    - Immune modulator

# NCI Cancer Antigen Pilot Prioritization Workshop

(October 23–24, 2008)

- Purpose: To develop a well-vetted ranked priority list of cancer vaccine target antigens based on pre-defined and pre-weighted objective criteria

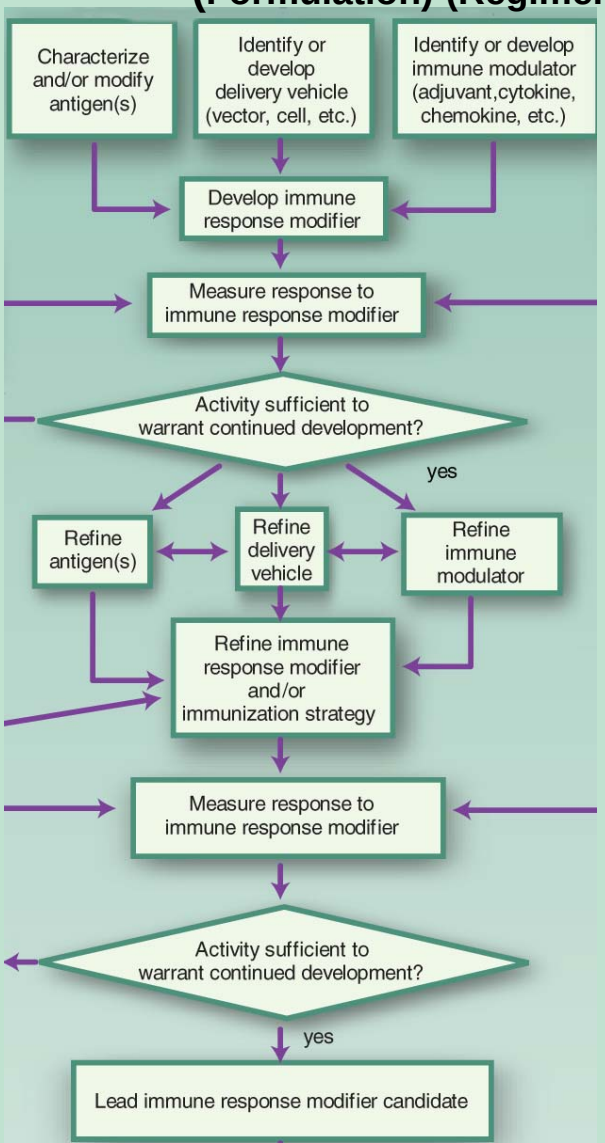
# NCI Workshop: Ranked 100 vaccine antigens

- Process
  - Developed list of “ideal” cancer antigen criteria/characteristics
    - 36 experts
  - Prioritized and weighted criteria using pair-wise comparisons
    - Web-based meeting (Decision Lens = consultants)
    - 20 experts
  - Selected 100 representative antigens
  - Garnered information on pre-defined criteria for each antigen from experts
    - ~60 experts
  - Ranked antigens based on the pre-defined pre-weighted objective criteria
    - 18 reviewers

# Immune Response Modifier Pathway:
## Creation of Modality

**Antigen – Delivery – IRM**

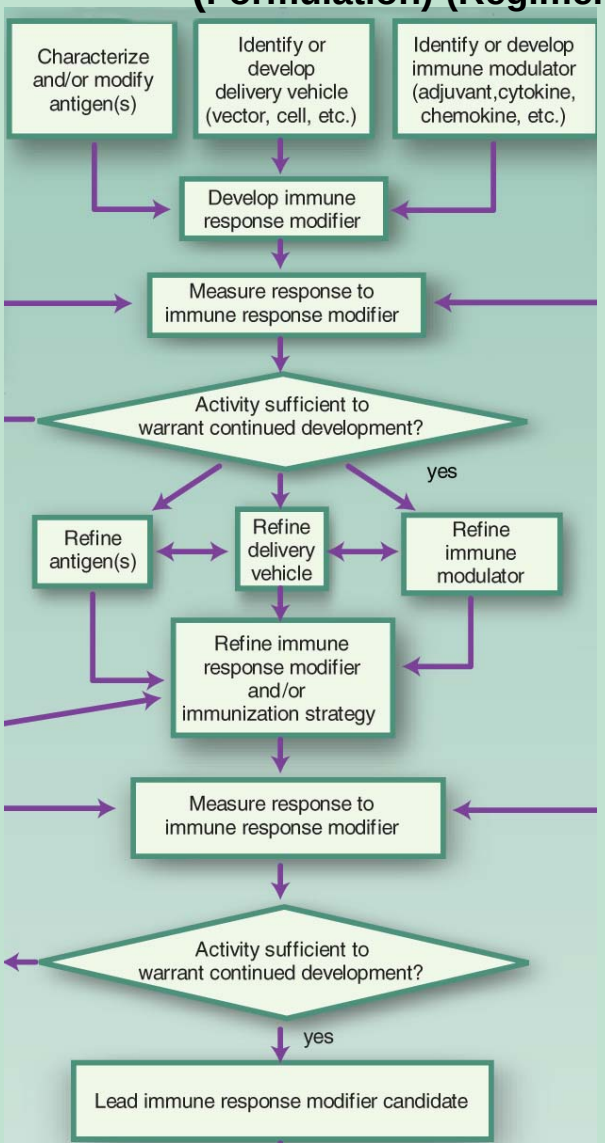
**(Formulation)-(Regimen)**




- **NCI Workshop for Pilot Prioritization of Antigens?**
- Workshop Criteria by Consensus
  - Antigen? [Criteria of "best" antigen]
    - Therapeutic Function
      - "Suggestive" evidence of clinical efficacy
    - >Immunogenicity
      - Immunogenic in clinical trials
    - >Specificity
      - Absolute specificity
    - >Oncogenicity
      - Oncogenic "self" protein
    - >Expression level & % positive cells
      - High level, all cancer cells
    - >Stem cell expression
      - Putative stem cell expression
    - >Number of patients with Ag positive cancers
      - Many patients/high expression
    - >Number of epitopes
      - Multiple epitopes
    - >Cellular location of expression
      - Cell surface and MHC expression, not shed

# Immune Response Modifier Pathway:
## Creation of Modality

**Antigen – Delivery – IRM**
**(Formulation)-(Regimen)**

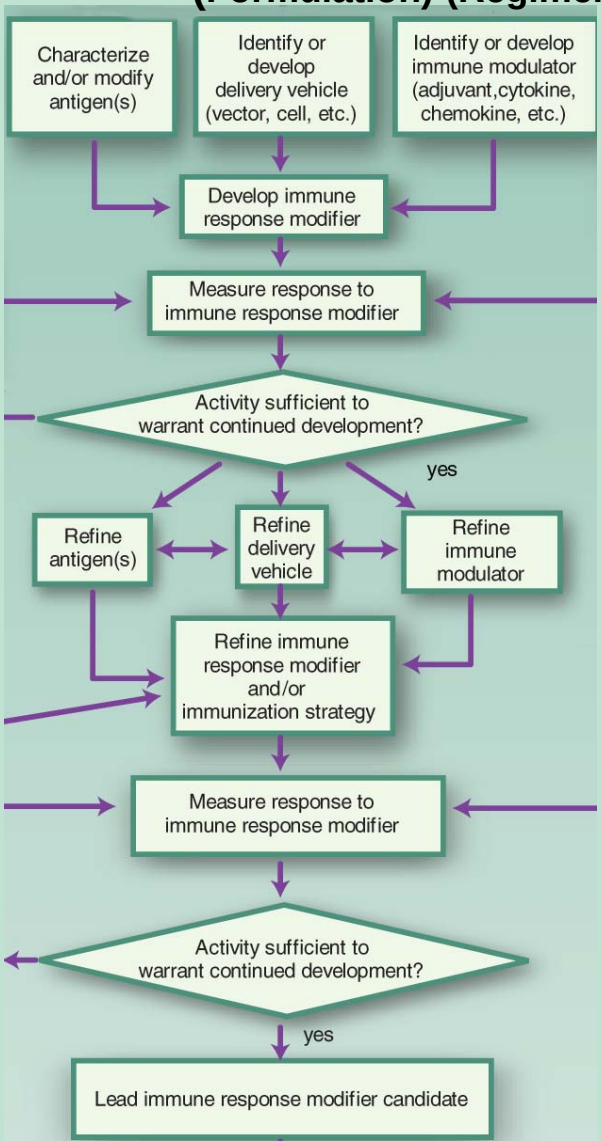



- Example of "Creation of Modality" "Vaccine using a shared antigen"
- Selected Antigen (as an Example Only)
  - **WT1 = Target Antigen**
    - Therapeutic Function
      - "Suggestive" evidence of clinical efficacy
    - Immunogenicity
      - Immunogenic in clinical trials
    - Specificity
      - Absolute specificity
    - Oncogenicity
      - Oncogenic "self" protein
    - Expression level & % positive cells
      - High level, all cancer cells
    - Stem cell expression
      - Putative stem cell expression
    - Number of patients with Ag positive cancers
      - Many patients/high expression
    - Number of epitopes
      - Multiple epitopes
    - Cellular location of expression
      - Cell surface and MHC expression
  - [Additional criteria - Target Disease = AML
    - Known to respond to T cell immunity

# Immune Response Modifier Pathway: Creation of Modality

**Antigen – Delivery – IRM**

**(Formulation)-(Regimen)**




- Example of "Creation of Modality" "Vaccine using a shared antigen"
- What vaccine has the highest potential for success?
  - Antigen? (One from the top of the priority list)
  - **Formulation?**
    - Delivery vehicle
    - Vector/cell/etc
    - **Adjuvant**
  - **Regimen?**
    - **Immune modulator**

# Prioritization of Agents: List of priority 20 agents with high potential for cancer therapy

- **T cell growth factors**
  - IL-7 (naïve T cells)
  - IL-15 (effector T cells)
- **DC activators**
  - Anti-CD40 & CD40L
- **DC growth factors to increase body burden of DC**
  - Flt3L
- **Vaccine adjuvants with immunotherapeutic potential**
  - IL-12
  - CpG
  - MPL
  - Poly I:C
  - Resiquimod & 852A
- **T cell stimulators**
  - 4-1-BB
  - Anti-GITR
  - Anti-OX40
- **T-cell attracting chemokines**
  - Adv-CCL21
- **Inhibitors of T cell checkpoint blockade**
  - Anti-PD1 & PD1Ligand
  - Anti–B7-H4
  - Anti–LAG-3
  - LIGHT
- **Inhibitors of cancer cell & immune cell suppression**
  - 1-methyl tryptophan (IDO inhibitor)
  - Anti-TGF-b
  - Anti-IL10 & anti-IL10R

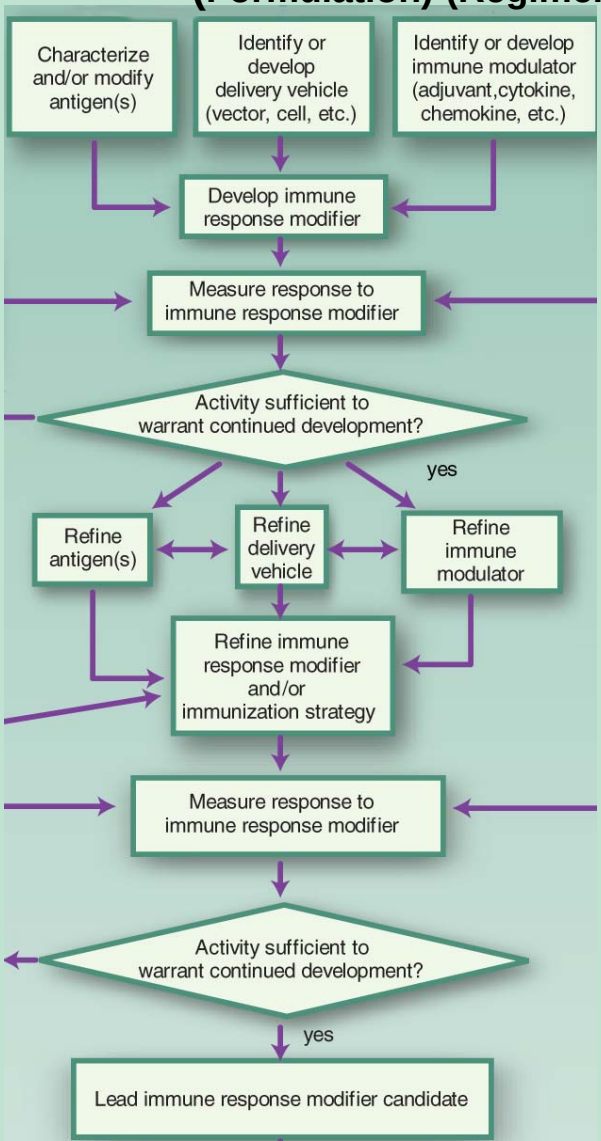
**[Anti-CTLA4 not considered, presumed to be approved in near future]**

http://web.ncifcrf.gov/research/brb/site/home.asp

# Immune Response Modifier Pathway:
## Creation of Modality

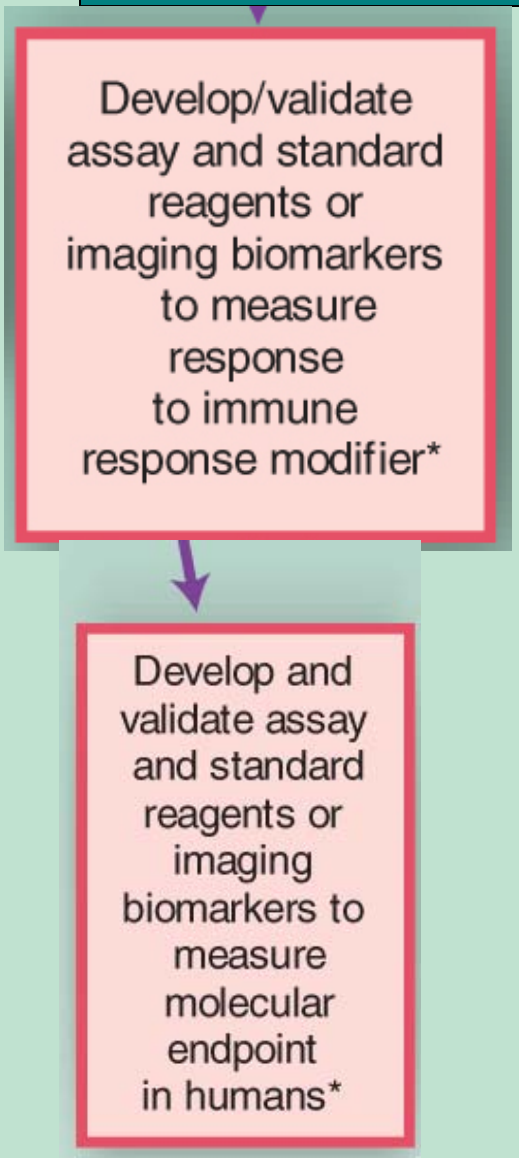
**Antigen** – **Delivery** – **IRM**

**(Formulation)-(Regimen)**



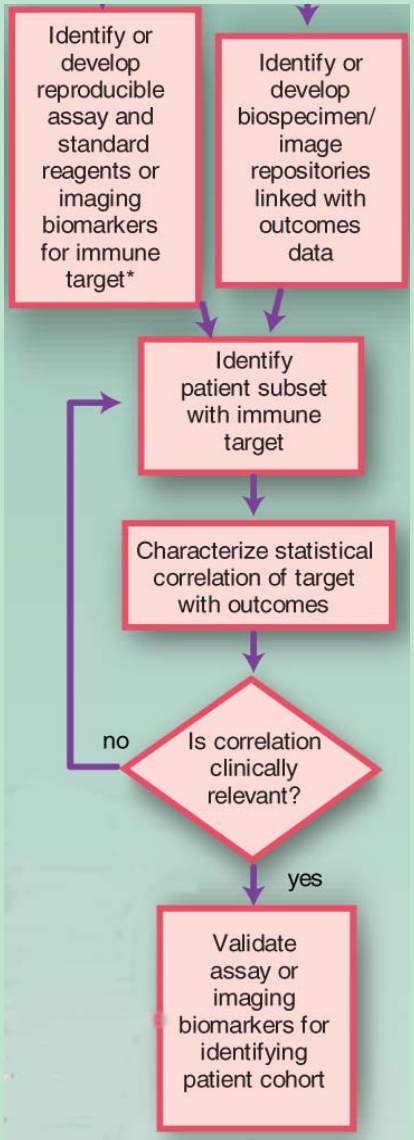

- Selected vaccine
  - Antigen
    - WT1
  - **Formulation (Need continued immunization)**
    - **Prime/Boos**t — DNA & Overlapping peptides, Or
    - Prime/Boost — Recombinant pox virus with co-stimulation molecules & Overlapping Peptides
    - Adjuvant(s) (From Agent list)
      - **CpG**
      - **MPL**
  - Regimen (Vaccine + IRM)
    - Immune modulators
      - **IL7 (Growth factor for naïve T cells and vaccine adjuvant)**
      - **Anti-PD1 (Inhibitor of T cell checkpoint blockade)**
  - Target cancer
    - AML in remission
    - Ovarian cancer in remission
    - “Easy remissions” — Common relapse

# Immune Response Modifier Pathway: Supporting tools: pharmacodynamic marker




- Immune assay
  - Direct immune response
    - T cell responses
      - T cell subset response
      - T cell response and subset in marrow
    - Antibody response
  - Spread immune response
    - Epitope spreading
    - Antigen spreading
- Tumor marker response
  - WT1 RT-PCR of PB & marrow
- Imaging assay
  - Hypoxia/blood flow/glucose metabolism/etc
  - 18F-deoxycytidine analog
    - [Radu et al (Witte) Nature Med 14:783, 2008]
- Therapy response
  - Time to progression

# Immune Response Modifier Pathway: Supporting tools: cohort marker



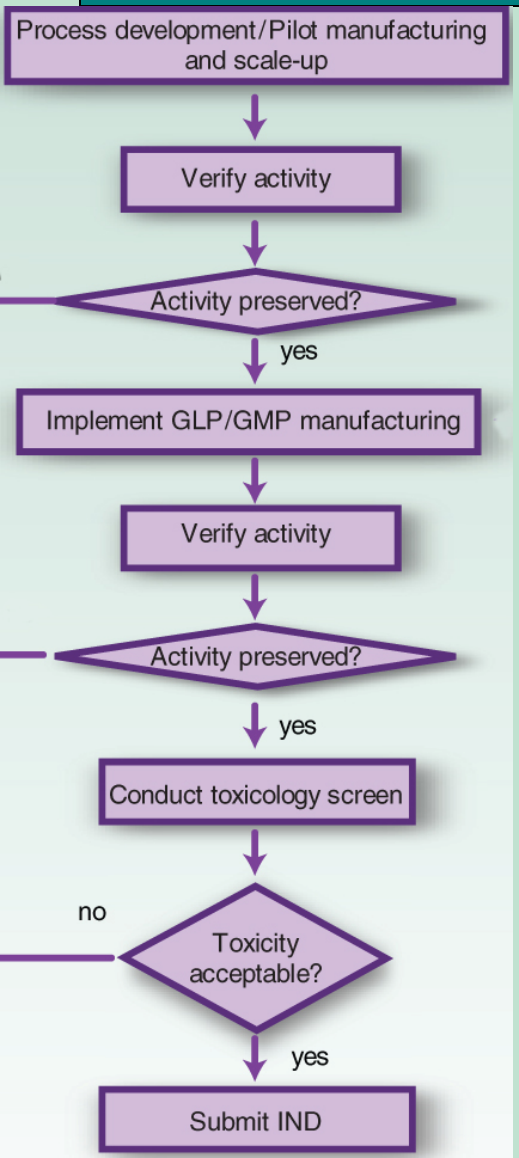

- Cohort marker = available
  - WT1 expression by tumor
    - RT-PCR
    - IHC

# Immune Response Modifier Pathway: Supporting tools: cell/animal model

Identify or develop clinically-relevant cell culture system and/or animal model

- Cells & animal models = available
  - Mouse models
    - Immunity in mice to mouse WT1 validated
    - Substantial tolerance
      - Similar to humans

# Immune Response Modifier Pathway: Preclinical Development



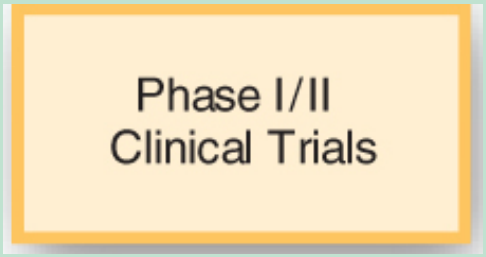

- Antigen = WT1
- Formulation
  - WT1 Overlapping Peptides
    - Available or easily manufactured
  - WT1 Plasmid
    - Truncated gene
    - Easily manufactured
  - Adjuvants (Manufactured — ?Available)
    - CpG
    - MPL
- Regimen
  - Immune Modulators (Manufactured — ?Available)
    - IL-7
    - Anti-PD1

# Immune Response Modifier Pathway: Clinical Trials

Phase I/II Clinical Trials

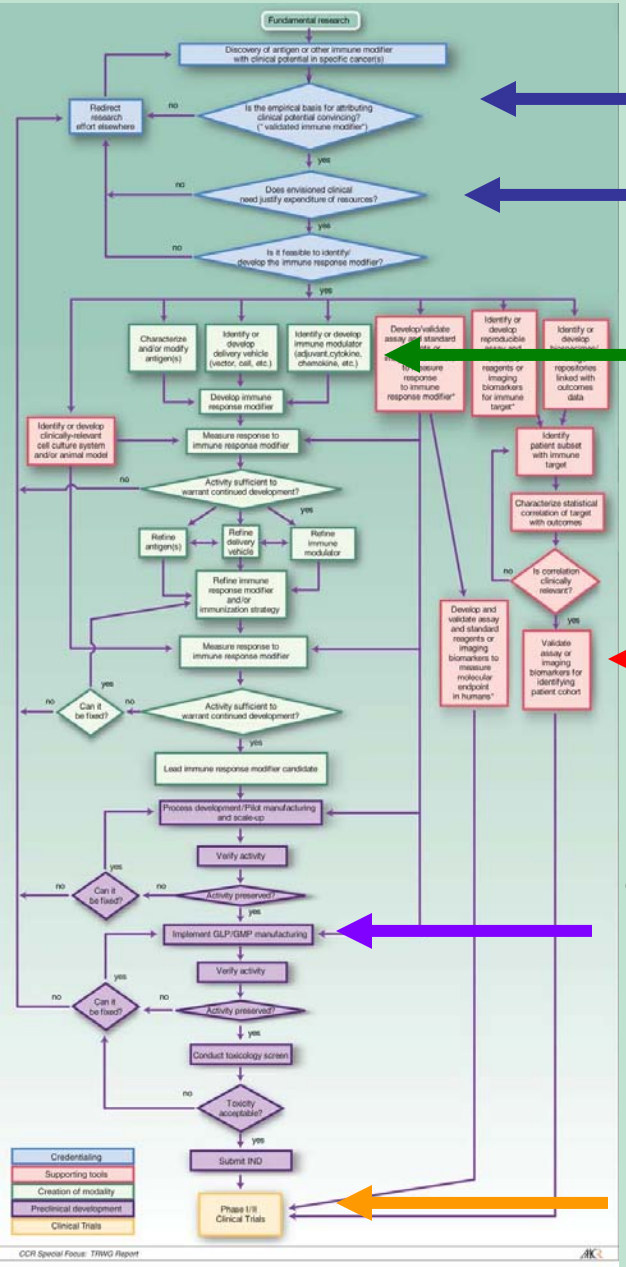
- Propose iterative Phase I trials with immunity, tumor marker & molecular imaging end points
  - Vaccine + adjuvants
    - (Prime/boost/boost/boost/boost/boost/ and on)
  - IL7 + vaccine + adjuvant
    (Iterative testing of vaccine pre/during/after IL7
  - Vaccine + adjuvants + anti-PD1
    (Iterative testing of dose/time/frequency
  - IL7 + vaccine + adjuvants + anti-PD1
- Phase II — only after achieving pre-defined level of immunity (T cell number and function)

# Immune Response Modifier Pathway: Clinical Trials




- Trials done best within a "Cancer Immunotherapy Network"
  - Key personnel & services for optimal trial design and trials
    - Protocol specialists, regulatory affairs, contracting, forms developer, statistician, etc.
  - Rapid set up & accrue
    - Experienced, preselected & precontracted trial sites
  - Optimal immune response data
    - Centralized laboratory for validated immune response data
  - Quality monitoring to assure quality outcome data
  - Adequate, on-time funding

# WT-1 vaccine in WT-1+ residual disease




- Ranks highly on antigen prioritization
- Relapse after CR occurs in most patients with AML & ovarian cancer
  - Priority Antigen: Peptides & plasmid formulation
  - Priority IRM as adjuvants (MPL/CpG)
  - Priority IRM to increase response IL-7 & anti-PD1
- Response monitoring
  - Immune = T cells and epitope spreading
  - Biomarker = WT1 PCR
  - Molecular Imaging = Activated T cell/blood flow
- Manufacture & testing of peptide, plasmid, IL-7 & anti-PD1 (NCI RAID with biotech/pharma)
- Iterative Phase I testing (NCI Cancer Immunotherapy Network)

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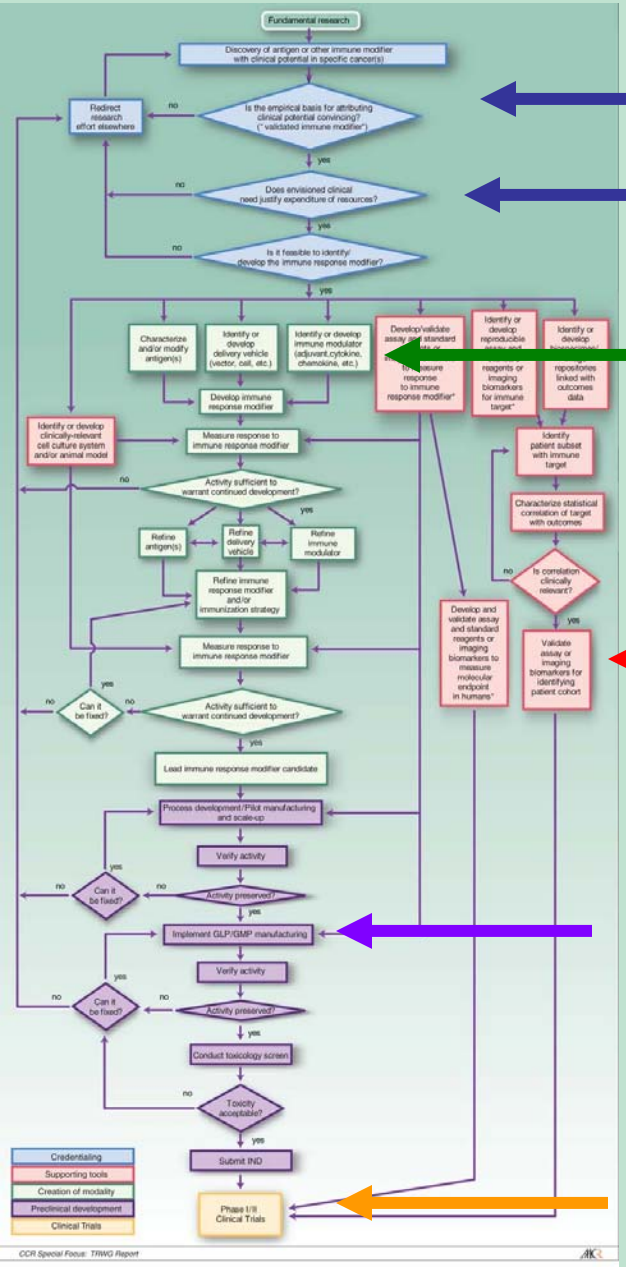


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